1   WHAT IS CLAIMED IS:

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3   1.   A method for inducing tolerance in a mammal to a pre-selected antigen comprising the

4   steps of

5   a.   isolating peripheral blood mononuclear cells (PBMC) from a whole blood sample

6   from said mammal;

7

8   b.   isolating dendritic cells from said PBMC;

9

10   c.   exposing said dendritic cells *ex vivo* to apoptotic cells expressing said pre-selected

11   antigen in the presence of at least one dendritic cell maturation stimulatory

12   molecule and in the absence of effective CD4+ T cell help;

13

14   d.   introducing a cellular portion of step c) into said mammal;

15

16   wherein said dendritic cells induce apoptosis of antigen-specific CD8+ T cells in said

17   mammal resulting in tolerance to said antigen.

18

19   2.   The method of claim 1 wherein said dendritic cell maturation stimulatory molecule is

20   PGE2, TNF-alpha, lipopolysaccharide, monocyte conditioned medium, CpG-DNA, or

21   any combination thereof.

22

1   3.   The method of claim 1 wherein said absence of effective CD4+ T cell is achieyed by

2   excluding CD4+ T cells from said step c). *non elected*

3

4   4.   The method of claim 1 wherein said absence of effective CD4+ T cell help is achieved by

5   including in step c) at least one agent that inhibits or eliminates effective CD4+ T cell

6   help.

7

8   5.   The method of claim 4 wherein said agent which inhibits or eliminates effective CD4+

9   help is a monoclonal antibody to a TNF superfamily member, a combination thereof, a

10   monoclonal antibody to a receptor for a TNF superfamily member, or a combination

11   thereof *non - elected*

12

13   6.   The method of claim 5 wherein said TNF superfamily member is CD40L, TRANCE,

14   OX40 or DR3.

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16   7.   The method of claim 5 wherein said receptor for a TNF superfamily member is CD40,

17   TRANCE, OX40 ligand or TWEAK.

18

19   8.   The method of claim 1 wherein said absence of effective CD4+ T cell is achieved by

20   inhibiting formation of mature forms of MHC II / peptide complexes within the dendritic

21   cell. *non elected*

22

1   9.   The method of claim 8 wherein said inhibiting is achieved by preventing cleavage of

2   invariant chain.

3

4   10.   The method of claim 9 wherein said preventing is achieved by addition of a cathepsin

5   inhibitors.

6

7   11.   The method of claim 8 wherein said inhibiting is achieved by blocking loading of

8   peptides by inhibiting HLA-DM.

9
10   12.   The method of claim 8 wherein said inhibiting is achieved by preventing successful

11   antigen degradation and formation of a MHC II peptide epitope.

12

13   13.   The method of claim 12 wherein said preventing is achieved by inhibiting cathepsin D or

14   alternative proteases.

15

16   14.   The method of claim 8 wherein said inhibiting is achieved by inhibiting transport of

17   MHC II / peptide complexes to the cells surface.   *non - deleted*

18

19   15.   The method of claim 4 wherein said agent which inhibits or eliminates effective CD4 T

20   cell help inhibits signalling consequent to dendritic cell-CD4 T cell engagement.

21

22   16.   The method of claim 15 wherein said agent is selected from a FKBP antagonist and a

23   TOR antagonist.

17. The method of claim 16 wherein said FKBP antagonist is FK-506.

2

3 18. The method of claim 16 wherein said TOR antagonist is rapamycin.

4

5 19. The method of claim 1 wherein said pre-selected antigen is a tumor antigen, a viral

6 antigen, a self antigen or a transplant antigen.

7

8 20. The method of claim 4 wherein said presence of at least one agent that inhibits effective

9 CD4 T cell help comprises a monoclonal antibody to TRANCE and FK-506.

10

11 21. The method of claim 1 wherein after a period of time following step c), a cellular portion

12 is infused into the mammal.

13

14 22. The method of claim 1 wherein said mammal is a human.

15

16 23. A method for inducing tolerance in a mammal to a pre-selected antigen comprising the

17 steps of

18 a. providing a dendritic cell chemoattractant at a site in a mammalian body, said

19 site comprising an antigen to which tolerization of an immune response is desired or

20 made to comprise an antigen to which tolerization of an immune response is desired

21 by administration of said antigen to said site; and

22

1   b.   administering to said site or systemically to said mammal an agent which

2   inhibits or eliminates effective CD4+ T cell help;

3

4   wherein immune system cells of said mammal are tolerized to said antigen.

5

6   24.   The method of claim 23 wherein said dendritic cell chemoattractant is a ligand for

7   CCR6.

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9   25.   The method of claim 23 wherein said ligand for CCR6 is 6-C-kine.

10

11   26.   The method of claim 23 wherein said agent which inhibits or eliminates effective

12   CD4+ help is a monoclonal antibody to a TNF superfamily member, a combination

13   thereof, a monoclonal antibody to a receptor for a TNF superfamily member, or a

14   combination thereof.

15

16   27.   The method of claim 26 wherein said TNF superfamily member is CD40L,

17   TRANCE, OX40 or DR3.

18

19   28.   The method of claim 26 wherein said receptor for a TNF superfamily member is

20   CD40, TRANCE, OX40 ligand or TWEAK.

21

1   29.   The method of claim 23 wherein said agent which inhibits or eliminates effective

2   CD4+ T cell inhibits formation of mature forms of MHC II / peptide complexes within the

3   dendritic cell.

4

5   30.   The method of claim 29 wherein said inhibits formation is achieved by preventing

6   cleavage of invariant chain.

7

8   31.   The method of claim 29 wherein said inhibits or eliminates is achieved by addition of

9   a cathepsin inhibitor.

10

11   32.   The method of claim 29 wherein said inhibiting is achieved by blocking loading of

12   peptides by inhibiting HLA-DM.

13

14   33.   The method of claim 32 wherein said inhibiting is achieved by preventing successful

15   antigen degradation and formation of a MHC II peptide epitope.

16

17   34.   The method of claim 33 wherein said preventing is achieved by inhibiting cathepsin

18   D or alternative proteases.

19

20   35.   The method of claim 29 wherein said inhibiting is achieved by inhibiting transport of

21   MHC II / peptide complexes to the cells surface.

22

1   36.   The method of claim 23 wherein said agent which inhibits or eliminates effective

2   CD4 T cell help inhibits signalling consequent to dendritic cell-CD4 T cell engagement.

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4   37.   The method of claim 36 wherein said agent is selected from a FKBP antagonist and a

5   TOR antagonist.

6

7   38.   The method of claim 37 wherein said FKBP antagonist is FK-506.

8

9   39.   The method of claim 37 wherein said TOR antagonist is rapamycin.

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11   40.   The method of claim 23 wherein said pre-selected antigen is a tumor antigen, a viral

12   antigen, a self antigen or a transplant antigen.

13

14   41.   The method of claim 23 wherein said presence of at least one agent that inhibits

15   effective CD4 T cell help comprises a monoclonal antibody to TRANCE and FK-506.

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